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Remarks

The Office Action mailed December 12, 2007, has been received and reviewed. Claim 3 having been canceled, without prejudice, the pending claims are claims 1-7, 9-13, and 30-39. Claims 5-7, 10, 12, and 35-39 being withdrawn from examination, as drawn to non-elected invention, claims 1, 2, 4, 9, 11, 13, and 30-34 are currently under examination. Reconsideration and withdrawal of the rejections are respectfully requested.

Applicants thank the Examiner for the rejoinder and examination of the claims of Group III (claims 32 and 43) and Group IV (claims 35 and 37) along with the claims of elected Group 1. On page 3 of the Office Action mailed December 12, 2007, the Examiner withdrew claims 5-7, 10, 12, and 35-39 "from consideration, as being drawn to non-elected species (*i.e.*, radiation therapy). Applicants do not understand. Claims 5-7, 10, 12, and 36, drawn to radiation therapy as the additional therapeutic agent, have already been fully searched and examined by the Examiner in the previous Office Action, mailed March 28, 2007. Applicants submit that it is improper to withdraw claims from consideration after the subject matter of the claims has been searched and examined (as demonstrated by the rejection of these claims in the previous Office Action mailed March 28, 2007). The rejoinder of claims 5-7, 10, 12, and 35-39 is requested.

Piecemeal Prosecution

MPEP 707.07(g) directs that "piecemeal examination should be avoided as much as possible." A first Office Actions on the merits was mailed March 28, 2007, rejecting the claims under 35 U.S.C. §102(b) and 35 U.S.C. §112, first paragraph. With the present, second nonfinal Office Action, mailed December 12, 2007, all of these rejections are withdrawn and the claims are newly rejected under 35 U.S.C. §103. Applicants do not understand why this rejection under 35 U.S.C. §103 was not included in the previous Office Action. Applicants express considerable concern with the apparent incremental, piecemeal prosecution of the present application and the added prosecution costs and time delays associated with such piecemeal prosecution.

Double Patenting Rejection

Claims 1-4, 9, 11, 13, 30-31, and 33 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-10 and 17-26 of co-pending application No. 10/780,150. Applicants respectfully request that this rejection be held in abeyance until the indication of otherwise allowable subject matter.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claim 3 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner asserted that the recitation "previously known" renders the claim unclear. Applicants respectfully disagree. However, to expedite prosecution, claim 3 has been canceled. The withdrawal of this rejection under 35 U.S.C. §112, second paragraph, is requested.

The 35 U.S.C. §103 Rejection

The Examiner rejected claims 1, 2, 4, 9, 11, 13, and 30-34 under 35 U.S.C. §103(a) as being unpatentable over WO 00/66764 and Tsung et al. (The Journal of Immunology, 1998, Vol. 160, pages 1369-1377, in view of Pinedo et al. (The Oncologist, 2000, Vol. 5, pages 497-500). This rejection is traversed.

"[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (*In re Kahn*, 441 F. 3d 977, 988 (CA Fed. 2006) cited with approval in *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385, 1396 (2007)). Applicants respectfully submit that a person of ordinary skill in the art having common sense at the time of the invention would not have reasonably considered combining the teachings of WO 00/66764, Tsung et al., and Pinedo et al. to obtain the claimed method of treating a subject with a cancer comprising administering an inhibitor of indoleamine-2,3-dioxygenase

(selected from the group consisting of 1-methyl-tryptophan, β-(3-benzofuranyl)-alanine, β-(3-benzo(b)thienyl)-alanine, and 6-nitro-D-tryptophan) and a cytotoxic antineoplastic chemotherapy agent. Further, Applicants submit that a person of ordinary skill in the art having common sense at the time of the invention would not have reasonably considered combining the teachings of WO 00/66764, Tsung et al. and Pinedo et al. to obtain the claimed method, wherein the administration of the inhibitor of indoleamine-2,3-dioxygenase and the cytotoxic antineoplastic chemotherapy agent demonstrate therapeutic synergy.

WO 00/66764

WO 00/66764 teaches administering tryptophan enhancing agents, including 1-methyl-tryptophan, β-(3-benzofuranyl)-alanine, and β-(3-benzo(b)thienyl)-alanine, to increase T cell proliferation *in vitro* and *in vivo* and to treat disorders characterized by constitutive expression of IDO (see, for example, abstract, page 2, lines 4-8 and 12-14, page 3, lines 30-34, and page 6, lines 17-25).

As acknowledged by the Examiner (page 6, Office Action mailed December 12, 2007), WO 00/66764 does not teach or suggest administering an IDO inhibitor along with a cytotoxic antineoplastic chemotherapeutic agent for the treatment of cancer, or that such administration results in a synergistic antitumor effect.

Rather, WO 00/66764 teaches treating cancer by administering a tryptophan enhancing agent along with one or more immune modulators selected from "antigen-specific T lymphocytes, peptide antigens, antigenic proteins and nucleic acids encoding peptide antigens" (page 3, lines 22-25 of WO 00/66764, see also page 16, lines 22-30), all of which "stimulate an immune response" (page 16, lines 22-30 of WO 00/66764). Applicants submit that such a teaching, of the additional administration of agents that "stimulate an immune response" provides no reason whatsoever to contemplate the administration an IDO inhibitor along with a cytotoxic antineoplastic chemotherapeutic agent for the treatment of cancer, and in fact, teaches away from combining IDO inhibitors with cytotoxic chemotherapeutic agents.

WO 00/66764 teaches that T cells can be cultured *in vitro* with a tryptophan enhancing agents "for expansion and eventual return to the subject . . . leading to lysis of antigen presenting cells, such as cancer cells" (page 15, lines 9-14). Further, WO 00/66764 teaches that cytokines that stimulate an immune response (such as IL-12 and GM-CSF) can also be used *in vitro*, along with tryptophan enhancing agents, to expand antigen responsive T cells *in vitro*, for subsequent administration of the expanded T cells into a patient for the treatment of cancer (page 17, lines 11-18 and page 16, lines 7-21).

Applicants submit that such teachings, of the *ex vivo* expansion of T cells with a tryptophan enhancing agent and optionally a cytokine provide no reason whatsoever to contemplate the administration an IDO inhibitor along with a cytotoxic antineoplastic chemotherapeutic agent to a subject for the treatment of cancer.

The Examiner asserted that "WO '764 contemplates that the inhibition of IDO can be used to increase a subject's immune response, leading to the lysis of antigen presenting cells, such as cancer cells which present one or more cancer associated antigens (page 15, lines 12-15)" (see page 5, Office Action mailed December 12, 2007 (emphasis in original)) and that the "[a]dministration of an IDO inhibitor to a cancer patient is suggested to increase a subject's immune response, leading to lysis of antigen presenting cells, such as cancer cells (WO '764, page 15, lines 12-14)" (see page 7, Office Action mailed December 12, 2007 (emphasis in original)). Applicants respectfully submit that these assertions are taken out of context and are incorrect. Applicants submit that the teachings of WO 00/66764 do not support the Examiner's assertion. Rather, the cited teachings of WO 00/66764 are limited to a method to enhance *in vitro* proliferation of cytotoxic T cells in the presence of tryptophan enhancing agents, and the subsequent treatment of cancer by adoptive cell transfer of such *in vitro* expanded cytotoxic T cells into the subject. Therefore, the increased increase in a subjects immune response and the lysis of antigen presenting cells to which the examiner refers to is not mediated by the administration of IDO inhibitors to a patient, but is the result of *ex vivo* expansion of T cells in the presence of tryptophan enhancing agents, that are subsequently transferred back to the subject

with cancer. This does not correlate with the claimed method. The reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a) is requested.

Tsung et al.

As noted by the Examiner, Tsung et al. teach the administration of a combination of IL-12 and cyclophosphamide ("Cy") for the treatment of cancerous sarcomas (see page 6, Office Action mailed December 12, 2007 and abstract of Tsung et al.). Further, Applicants submit that Tsung et al. teach "tumors that are refractory to treatment by either IL-12 or Cy alone can be completely eradicated by the combination of Cy and IL-12. *IL-12 is apparently the only cytokine capable of mediating tumor eradication*, and the effect is dependent on IFN-γ" (abstract of Tsung et al. (emphasis added)). Tsung et al. also teach that *IL-12 plays an essential and unique role in the effectiveness of the combination treatment*; "other cytokines (IL-2, IL-4, and IL-10) combined with Cy did not have similar antitumor effects" (page 1375, column 2 of Tsung et al. (emphasis added)). The effectiveness of "*the combination of CY and IL-12 . . . represents a novel observation . . . based on the biologic activity of IL-12*" (page 1375, column 2 of Tsung et al. (emphasis added)) and that "the role of Cy is to facilitate the onset of an IL-12 dependent Th1 response" (see page 1376, column 1 of Tsung et al.).

Applicants respectfully submit that Tsung et al. clearly teach that the antitumor effectiveness of their method is based on the biologic activity of IL-12 and is unique to the specific combination of only IL-12 and cyclophosphamide. Applicants respectfully submit that a person of ordinary skill in the art having common sense at the time of the invention would not have reasonably considered combining the teachings of WO 00/66764 with the teachings of Tsung et al., to obtain a method of treating cancer comprising the administration of an inhibitor of IDO and a cytotoxic antineoplastic agent. In fact, Applicants respectfully submit that the teachings of Tsung et al. teach away from considering any modification whatsoever of a method of treating cancer by the administration of IL-12 and cyclophosphamide.

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Other than asserting that "Tsung et al. teach that a combination of IL-12 and the cytotoxic agent cyclophosphamide completely eradicates . . . sarcomas that are refractory to treatment with either IL-12 or cyclophosphamide alone, thus motivating combining these agents for treating sarcomas," the Examiner articulates no rationale for combining the teachings of WO 00/66764 and Tsung et al. (see middle paragraph, page 6, Office Action mailed December 12, 2007). Applicants submit that a person of ordinary skill in the art having common sense at the time of the invention could not have reasonably considered combining the teachings of WO 00/66764 and Tsung et al.

Applicants submit that a person of ordinary skill in the art at the time of the invention would not have a reasonable expectation of success in combining the teachings of WO 00/66764 and Tsung et al. The Examiner's position is apparently that the teachings of Tsung et al. complement the teachings of WO 00/66764 and, thus, one skilled in the art would have reason to expect that the combination of IDO inhibitors with an immunopotentiating agent, such as cyclophosphamide, would result in enhanced T cell proliferation and would demonstrate a concomitant antitumor effect. Applicants submit that this is incorrect.

First, the Examiner's assertion that cyclophosphamide is an immunopotentiating agent that would result in increased T cell proliferation is incorrect. Rather, it is widely known to those of skill in the art that cyclophosphamide is an immunosuppressive agent, and not an agent that potentiates an immune response. It is administered clinically to patients to suppress immune responses, including autoimmune reactions and transplant rejection reactions. Specifically, cyclophosphamide "slows the growth of cancer cells by interfering with the actions of deoxyribonucleic acid (DNA) within the cancerous cells. It is, therefore, referred to as a cytotoxic drug. Unfortunately, normal cells also are affected, and this results in serious side effects. Cytoxan also suppresses the immune system and is also referred to as immunosuppressive" (Medicinenet.com web entry for cyclophosphamide (copy provided with PTO-1449 submitted herewith). See also, Reiner et al., *Blood* 85(1995):351-358, Moyo et al.,

Blood 100 (2002):704-706, Nygaard and Lovik, *Toxicology* 174 (2002):153-161, and Hou et al., *Environmental Toxicology and Pharmacology* 24 (2007):30-36.

Further, as demonstrated by Tsung et al., the combination of any immunostimulatory agent with cyclophosphamide does not necessarily result in an enhanced immune reaction against tumors. Specifically, Tsung et al. teach that the combination of IL-2, IL-4 or IL-10 with cyclophosphamide does not result in any enhancement of antitumor effect. Tsung et al. teaches that only the cytokine IL-12 in combination with only cyclophosphamide results in an enhanced antitumor effect. Moreover, the results of Tsung were not reproduced with other chemotherapeutic agent such as 5-FU, so a person skilled in the art would not infer from the teachings of Tsung that the combination of ANY antineoplastic agent with IL-12 would be expected to yield an effective antitumor response. Thus, one of skill in the art would have no reason to expect the effectiveness of the combination of an IDO inhibitor and cytotoxic antineoplastic chemotherapy agent.

Applicants submit, for the reasons discussed above, that one of skill in the art would not infer from the teachings of WO 00/66764 or Tsung et al. that the combination of an IDO inhibitor and a cytotoxic antineoplastic chemotherapy agent would be expected to yield an effective antitumor response, or that the administration of theses two agents would demonstrate therapeutic synergy.

The reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a) is requested.

Pinedo et al.

Pinedo et al. teach neoadjuvant chemotherapy with the combination of doxorubicin, cyclophosphamide and GM-CSF followed by surgery and postoperative radiation therapy for the treatment of breast cancer (see abstract of Pinedo et al.) Neoadjuvant chemotherapy is chemotherapy that is administered prior to a surgical procedure (see, for example, "Chemotherapy Before Breast Cancer is Valuable," Cancerwise, July 2005 (copy provided with

PTO 14-49 filed herewith)). Thus, Pinedo teach a complex, multi-step method of treating cancer that comprises 1) administering the two chemotherapy agents doxorubicin and cyclophosphamide along with the cytokine GM-CSF, followed by 2) surgery to remove the tumor, which is then followed by 3) postoperative radiation therapy.

In the method of Pinedo et al., the combination of doxorubicin (also known as adriamycin) and cyclophosphamide (also known as cytoxan) was administered as this specific combination "has long been considered a standard adjuvant chemotherapy combination for the treatment of breast cancer" ("Taxotere®/Cytoxan® Superior to Standard Adriamycin®/Cytoxan as Adjuvant Therapy in Breast Cancer," copy provided with PTO-1449 submitted herewith). As discussed earlier, cyclophosphamide "slows the growth of cancer cells by interfering with the actions of deoxyribonucleic acid (DNA) within the cancerous cells . . . Unfortunately, normal cells also are affected, and this results in serious side effects. Cytoxan also suppresses the immune system and is also referred to as immunosuppressive" (Medicinenet.com web entry for cyclophosphamide (copy provided with PTO-1449 submitted herewith).

Pinedo et al. teach that "GM-CSF was chosen . . . because of its additional immunostimulatory and potential angiogenic effects. . . . [and] hypothesized that . . . the long term administration of GM-CSF . . . might give rise to tumor-specific cytotoxic T-cell responses" (page 498, column 1, Pinedo et al.). Pinedo et al. "suggest a role for GM-CSF in the generation of circulating angiogenesis inhibitor" which inhibits tumor metastasis (page 499, column 1, Pinedo et al.), and note that "the recruitment and maturation of dendritic cells induced by GM-CSF may lead to increased levels of . . . IL-12," a cytokine that "has been previously shown both to direct the initiation of effective cell-mediated antitumor immune responses and exhibit considerable angiogenic effects" (page 499, bridging columns 1 and 2, Pinedo et al.).

Applicants submit that Pinedo et al. teach a complicated, multi-step method for treating cancer. One of skill in the art would have no reason whatsoever to combine the multi-step method of Pinedo et al. With the methods of WO 00/66764 and/or Tsung et al. One of skill in the art would have no reason whatsoever to remove a single component of such a multi-step

method, such as the administration of cyclophosphamide, to combine with the administration of an inhibitor of IDO, as taught in WO 00/66764. Further, Pinedo et al. specifically selected GM-CSF to be added to the combined chemotherapy regime of doxorubicin *and* cyclophosphamide prior to surgery and radiation therapy *because of its immunostimulatory and angiogenic effects*, and that "GM-CSF not only recruits dendritic cells from the bone marrow, but also stimulates their maturation and activation to acquire their maximum ability to prime cytotoxic T cells" (column 2, page 498, Pinedo et al.).

The Office Action provides no rationale or motivation for combining the teachings of Pinedo et al. with WO 00/66764 and Tsung et al. Applicants respectfully submit that a person of ordinary skill in the art having common sense at the time of the invention would not have reasonably considered combining the teachings of Pinedo et al. (of a complicated, multi-step method for the treatment of breast cancer, in which it is hypothesized that GM-CSF impacts the function of dendritic cells) with the teachings of WO 00/66764 (of the administration of IDO inhibitors for the treatment of cancers that constitutively express IDO) or with the teachings of Tsung et al. (of the unique and novel effectiveness of IL-12 and cyclophosphamide for the treatment of cancer), to obtain a method of treating cancer comprising the administration of an inhibitor of IDO and a cytotoxic antineoplastic agent. Reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a).

The Examiner asserted that "Pinedo et al. discuss biological concepts of prolonged neoadjuvant treatment plus GM-CSF in locally advanced tumors, [and] in patients with locally advanced breast cancer, a dysfunction of dendritic cells leads to a general immunosuppressive state with depressed T-cell reactivity. Chemotherapy is disclosed to reduce the production of tumor-derived immunosuppressive factors, enabling the initiation of tumor-specific cytotoxic T-cell responses as well as to induce tumor cell necrosis and apoptosis, both of which cause antigen release" (page 6, Office Action mailed December 12, 2007 (citations omitted) (emphasis in original)). Applicants respectfully submit that these general biological concepts presented by Pinedo et al. would in no way whatsoever lead one of skill in the art to contemplate combining

the teachings of WO 00/66764, Tsung et al., and Pinedo et al. to obtain the claimed method of treating cancer by administering an inhibitor of IDO and an antineoplastic chemotherapeutic agent. Further, from the teachings of Pinedo et al. one of skill in the art would have no reasonable expectation of success in administering an inhibitor of IDO and an antineoplastic chemotherapeutic agent in a method of treating cancer and no expectation that the administration of theses two agents would demonstrate therapeutic synergy.

First, statements such as "general immunosuppressive state" or "tumor-derived immunosuppressive factors," are very general statements that do not identify any of the possible numerous immune mechanisms at work in Pinedo et al. and do not provide any guidance to design therapeutic strategies based on specific mechanistic considerations.

Second, when defining this immunosuppressive state, Pinedo et al. cite the works of references 16-22, which lead the reader to interpret that the immunosuppressive mechanisms the authors are referring to are based on mechanisms that involve: 1) decreased antigen presentation by dendritic cells, 2) immunosuppressive mechanisms caused by increased levels of TGF-β in the tumor microenvironment, and 3) the disablement of the immune system by tumor-derived cytokines, such as IL-4, IL-10, TGF-β, IL-6 and VEGF, that have been shown to inhibit dendritic cell maturation (see, for example, col. 2, page 498 of Pinedo et al.). The discussion by Pinedo et al. fails to teach any role for IDO or inhibitors of IDO in effecting a "general immunosuppressive state."

At best, Pinedo et al. suggests that chemotherapy in combination with long-term administration of GM-CSF initiates a series of mechanism that can overcome apparent failures in the immune system. The teachings of Pinedo et al. would lead a person skilled in the art to use strategies that involve suppression or neutralization of tumor-derived immunosuppressive cytokines, such as TGF-β, VEGF, IL-4 and IL-10, to counteract the immunosuppressive effect of the tumor.

Thus, a person skilled in the art would not relate the immunosuppressive mechanisms taking place in the tumor microenvironment (which Pinedo et al. teach are dominated by

cytokines that cause arrest in dendritic cell maturation and defects in antigen presentation) with immunosuppressive mechanisms mediated by IDO^+ dendritic cells in the tumor draining lymph node, as with the present invention.

Reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a).

No Reasonable Expectation of Success

Applicants submit that each of the methods taught by WO 00/66764, Tsung et al., and Pinedo et al. are hypothesized to be impacting different arms of the immune system. Applicants respectfully submit that it defies logic to pick and choose from these teachings, pertaining to different functional aspects of the immune system.

WO 00/66764 suggest the combination of IDO inhibitors with immunostimulating agents. As antineoplastic chemotherapeutic agents are not particularly known to be immunostimulating, but on the contrary, are known to cause immunosuppression, one of skill in the art would not be lead to think that chemotherapeutic agents could be used as one of the immunostimulating agents taught by WO 00/66764.

The teachings of Tsung et al. demonstrate that cyclophosphamide alone does not have an antitumor effect, but that the specific combination of only IL-12 with only cyclophosphamide is required to observe an antitumor effect. Thus, one of skill in the art would not be lead to administer cyclophosphamide along with an IDO inhibitor.

Finally, Pinedo et al. teach that in order to elicit an immune response following prolonged neoadjuvant therapy the administration of GM-CSF locally is required to recruit and activate dendritic cells that could initiate an immune response. Thus, one of skill in the art would not be lead to administer cyclophosphamide along with an IDO inhibitor.

Applicants submit that the Examiner has used improper hindsight to pick and choose from the teachings of WO 00/66764, Tsung et al., and Pinedo et al., to assert that the combined teachings teach the claimed method of administering an IDO inhibitor and an antineoplastic chemotherapy agent.

The Examiner asserted that "the skilled artisan would have been imbued with at least a reasonable expectation that administration of 1-methyl-tryptophan and cyclophosphamide, optionally combined with a cytokine, would result in an effective treatment of cancer" (page 8, Office Action mailed December 27, 2007). Applicants respectfully disagree. In the field of cancer immunotherapy a complex network of molecular mechanisms, both characterized and uncharacterized, are at play. These molecular interactions take place on different cell types and at different points in time. Even for the most skilled persons in the art, it is not obvious to infer ahead of time that a proposed combination of immune treatments will result in a desired or predicted effect, based on the effectiveness or mechanism of action of the individual components or on the demonstrated effectiveness of a different combination of components. Each of WO 00/66764, Tsung et al., and Pinedo et al. teach different methods that involve a different combination of different components and steps, the specific combination of which is necessary for a successful outcome. Applicants submit that one of skill in the art would not have a reasonable expectation of success with new combinations of individual components or steps taken from each of WO 00/66764, Tsung et al., and Pinedo et al. Further, in view of the absence of a proper *prima facie* case articulating a rational reason for combining the cited teachings to obtain the claimed invention, a reasonable expectation of success is putting the cart before the horse.

Further, Applicants submit that from the combinations of the varied teachings extracted by the Examiner from WO 00/66764, Tsung et al., and Pinedo et al., a person skilled in the art would not reach to the conclusion that administration of IDO inhibitors in combination with antineoplastic chemotherapeutic agents would have a synergistic effect.

In view of the above discussion, the reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a) is requested.

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Amendment and Response
Serial No.: 10/780,797
Confirmation No.: 1508
Filed: February 17, 2004
For: USE OF INHIBITORS OF INDOLEAMINE-2,-DIOXYGENASE IN COMBINATION WITH OTHER THERAPEUTIC MODALITIES

Summary

It is respectfully submitted that the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted
By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

April 14, 2008
Date

By: Nancy A. Johnson
Nancy A. Johnson
Reg. No. 47,266
Direct Dial (612) 305-4723

CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to **Mail Stop Amendment**, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 14 day of April, 2007, at 11:40 A.M. (Central Time).

By: Sandy Truehart
Name: Sandy Truehart